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(12) # EUROPEAN PATENT APPLICATION

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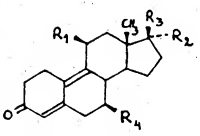
(54) **New 11-arylsteroid compounds.**

(57) The invention relates to new 11-arylsteroid compounds, having a strong antiprogestin and a weak or nonexistent antiglucocorticoid activity, to processes for preparing said compounds and also to pharmaceutical preparations which contain these derivatives as active constituent, characterized in that said steroids have the following formula:



in which
R_1 is an aryl group with a - N(Y)—X
group as substituent, X and Y each being separately H or a (1-4 C) hydrocarbyl group or together a (2-6 C) hydrocarbyl group which forms a 3- to 7-membered ring together with the nitrogen atom;
R_2 is hydrogen, hydroxyl, an acyloxy or an alkoxy group or a saturated or unsaturated d hydrocarbyl

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group containing 1-8 carbon atoms, which hydrocarbyl group is provided with at least one hydroxyl, oxo, azido, cyano and/or halogen group;

R_3 is a hydroxyl, an acyloxy or an alkoxy group or an acyl group optionally substituted by a hydroxyl, alkoxy, acyloxy or halogen group; or R_2 and R_3 together form a ring system, with the proviso that if R_3 is hydroxyl, R_2 is not hydrogen or hydroxyl; and

R_4 is a methyl or ethyl group;

and the α- and β-bonds are indicated by dashed (---) and wedged (◄) lines respectively.

New 11-arylst r Id compounds

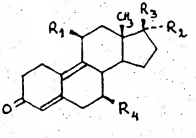
The invention relates to new 11-arylsteroid compounds, to processes for preparing said compounds and also to pharmaceutical preparations which contain these derivatives as active constituent.

The antiprogestins include, inter alia, substances which have affinity for the progesterone receptor, such substances not exerting, or exerting to a considerably reduced extent, the action of progesterone. Progesterone is involved, inter alia, in the nidation of a fertilized egg cell in the uterus wall. It will be possible to prevent the nidation by occupying the receptor sites in the uterus cells with antiprogestins, as a result of which the pregnancy can be terminated at a very early stage. The antiprogestins further include progesterone synthesis inhibitors. Antiprogestins are known from the U.K. Patent Application GB 2175905 and PCT Patent Application WO 87/05908.

However, it has emerged that in addition to the desired antiprogestin activity, such antiprogestins also have an antiglucocorticoid activity which is undesirable if these substances are used as a pregnancy-terminating agent, as drug against endometriosis or as drug against steroid hormone dependent cancers, such as breast, endometrium and vagina cancer.

A new group of compounds has now been found which have a strong antiprogestin and a weak or nonexistent antiglucocorticoid activity.

The invention therefore relates to said steroids, characterized in that said steroids have the following formula:



in which

R_1 is an aryl group with a - N(Y)—X group as substituent, X and Y each being separately H or a (1-4 C) hydrocarbyl group or together a (2-6 C) hydrocarbyl group which forms a 3- to 7-membered ring together with the nitrogen atom;

R_2 is hydrogen, hydroxyl, an acyloxy or an alkoxy group or a saturated or unsaturated hydrocarbyl group containing 1-8 carbon atoms, which hydrocarbyl group is provided with at least one hydroxyl, oxo, azido, cyano and/or halogen group;

R_3 is a hydroxyl, an acyloxy or an alkoxy group or an acyl group optionally substituted by a hydroxyl, alkoxy, acyloxy or halogen group; or R_2 and R_3 together form a ring system, with the proviso that if R_3 is hydroxyl, R_2 is not hydrogen or hydroxyl; and

R_4 is a methyl or ethyl group;

and the α- and β-bonds are indicated by dashed (---) and wedged (◄) lines respectively.

The aryl group in R_1 may be derived from, for example, benzene, biphenyl, napthalene, anthracene or phenanthrene. A phenyl group is the most preferred. In the case of a phenyl group, the substituent is preferably in the meta or para position.

The substituent on the aryl group is a group having the formula

The (1-4 C) hydrocarbyl group X and Y may b , inter alia, methyl, ethyl, vinyl, ethinyl, propyl, 2-

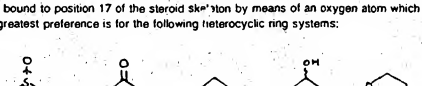
propenyl, allenyl, 1-propynyl, butyl and branched analogues thereof. If X and Y together form a (2-6 C) hydrocarbyl group, the hydrocarbyl group may be saturated or unsaturated; preferably the hydrocarbyl group contains 4 or 5 carbon atoms. Preferably, X and Y are a saturated alkyl group containing 1-3 carbon atoms and, with still more preference, methyl.

The (1 - 8 C) hydrocarbyl group R_2 which is provided with at least one hydroxyl, oxo, azido, cyano and/or halogen group may be, inter alia, 3-hydroxy-1-propynyl, 3-hydroxy-1-propenyl, chloroethinyl, bromoethinyl, 3-hydroxypropyl and methyloxymethyl. The acyloxy group R_2 and R_3 is preferably derived from an organic carboxylic acid containing 1-18 carbon atoms, such as acetic acid, propionic acid, butyric acid, trimethylacetic acid, phenylacetic acid, cyclopentylpropionic acid, phenylpropionic acid, valeric acid, caproic acid, pelargonic acid, lauric acid, palmitic acid, benzoic acid or succinic acid.

With the term alkoxy group in the definition of R_2 and R_3 is preferably meant an unsubstituted or substituted alkoxy group containing 1-12 carbon atoms, such as, for example, methoxy, ethoxy, cyclopentyloxy, benzyloxy and tetrahydropyranyloxy.

The acyl group R_3 optionally substituted by a hydroxyl, alkoxy, acyloxy or halogen group is preferably derived from an organic carboxylic acid containing 1-18 carbon atoms, such as those already mentioned above. Examples of suitable substituted acyl groups are hydroxyacetyl, fluoroacetyl, chloroacetyl and propionyloxyacetyl.

If R_2 and R_3 together represent a ring system, the preference is for heterocyclic 5- or 6-ring systems, the ring being bound to position 17 of the steroid skeleton by means of an oxygen atom which forms part of the ring. The greatest preference is for the following heterocyclic ring systems:



the carbon atom which is provided with an * being the carbon atom at position 17 of the steroid skeleton.

For R_2, the greatest preference is for a saturated or unsaturated alkyl group containing 1-4 carbon atoms substituted at least by one hydroxyl or oxo group and for R_3 it is for a hydroxyl group, a (1-6 C) acyloxy or a (1-6 C) alkoxy group if R_2 and R_3 do not together form a ring system. With still more preference, R_2 is then an unsaturated alkyl group containing 1-4 carbon atoms and having 1 or 2 hydroxyl groups.

The invention also relates to pharmaceutical preparations which contain one ore more of the compounds according to the invention as active constituent. The new compounds may be administered in the usual manner orally, intravaginally or parenterally in combination with pharmaceutical auxiliary substances in the form of tablets, pills, dragées and other normal dispensing forms. The dosage forms may be prepared by known galenic procedures.

The compounds according to the present invention may be prepared starting from 7β-methyl-3,17-dioxoandrost-4-en-19-al or an equivalent 7β-R_4 compound.

Said compounds are converted by analogy with the method for converting the corresponding 7α-methyl compound into 17β-hydroxy-7α-methyl-19-nor-17α-pregn-5(10)-en-20-yn-3-one as described in Receuil des Traveaux Chimiques des Pays-Bas 105 (1986),111-115, into 17β-hydroxy-7β-methyl-17α-R_2-oestr-5(10)-en-3-one or an equivalent 7β-R_4 compound. After bromination and dehydrobromination, for example, with phenyltrimethylammonium tribromide and pyridine to the corresponding Δ^4, Δ^3-dienes, said compounds are ketalized to the $\Delta^{5(10)}$, $\Delta^{9(11)}$-3-ketal. The ketal group has the formula:

R_5 and R_6 representing an alkyl group containing 1-4 carbon atoms or R_5 and R_6 together forming an alkylene group containing 2-5 carbon atoms and * specifying the carbon atom in position 3 of the steroid skeleton. The ketalization can be carried out in an R_5OH alcohol in the presence of an acid as catalyst; in this case, R_4 is identical to R_5. If the reaction is carried out in the presence of a diol, a ketal is obtained in

which R_5 and R_6 together form an alkylene group.

Starting from said 3-ketal compounds, the group in position 11 can then be additionally introduced into the steroid skeleton.

Thus, after epoxidation of the $\Delta^{5(10)}$ double bond, for example with m-chloroperbenzoic acid in CH_2Cl_2 and $NaHCO_3$, the R_1 group can be introduced with the simultaneous formation of an OH group in position 5 and the rearrangement of the double bond from 9(11) to 9(10) by reaction with an R_1-metal-X compound containing R_1, X being a halogen atom, such as R_1MgBr, for example in the presence of CuCl in tetrahydrofuran or with an R_1Li compound. After the introduction of R_1, dehydration and hydrolysis may be carried out immediately (for example, in 80% acetic acid at 75 °C or in 2N HCl in acetone); in that case, compounds are obtained which contain 17α-R_2 and 17β-OH.

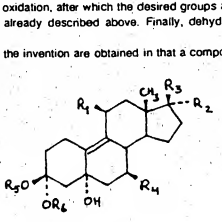
If R_2 or R_3 is an OH group, said group may, if desired, be esterified or etherified by methods known per se before or after introducing the R_2 group or after dehydration and hydrolysis.

For the preparation of compounds in which R_2 and R_3 together form a ring system, the process proceeds analogously to the method already described, provided that R_2 is an oxygen-containing group in which the oxygen atom is protected by means of a hydrolysable group. The group used according to this variant on 17α is preferably an alkyl, alkenyl or alkynyl ether. The greatest preference is for groups having a terminal tetrahydropyranyl group. After introducing group R_1, unsaturated bonds optionally present in the group introduced at 17α are reduced if desired. Subsequently, dehydration and hydrolysis is carried out with the protective groups in the 17α substituent being split off simultaneously to form compounds containing t7β-OH, 17α-R_2. In the step in which a part of the group introduced at t7α is split off, preferably the ether group and, with still more preference, the tetrahydropyranyl group is split off to form an alkyl, alkenyl or alkynyl group with a terminal hydroxyl group. This group is finally cyclized with the t7β-OH group by processes known per se.

For the preparation of compounds according to the general formula, the starting point may be a 3-methoxy-7β-R_5-18-(1-3 C)-alkyloestra-1,3,5-trien-17β-ol. After Birch reduction (which yields Δ^2, $\Delta^{5(10)}$), Oppenauer oxidation (which yields t7-keto) and reaction with a weak acid (which yields 3-keto, $\Delta^{5(10)}$), a compound is obtained having the formula as shown for compound 11 in the said Receuil paper, provided that 7α-CH_3 is replaced by 7β-R_4 and that 13-CH_3 is replaced by 13-(2-4 C)alkyl.

Another method for the preparation of compounds according to the invention is that in which group R_1 is first introduced in position t1 and subsequently the functional groups are incorporated at 17. Starting from compounds having formula 11 in the Receuil paper, provided that 7α-CH_3 is replaced by 7β-R_4 after ketalization to the 3-ketal as already described, the 17-keto group is protected, for example by reduction with sodium borohydride to a hydroxyl group. After deketalization, bromination, dehydrobromination, ketalization of the 3-keto group and epoxidation, group R_1 can be introduced in position 11. Subsequently, the 17-keto group is reformed by oxidation, after which the desired groups are introduced at 17α and 17β in a manner known per se and as already described above. Finally, dehydration and hydrolysis has to be carried out.

The compounds according to the invention are obtained in that a compound having the formula:



in which R_1, R_2, R_3, R_4, R_5, and R_6 have the same meaning as has already been described, provided that, if R_2 and/or R_3 represent an oxygen-containing group, R_2 and/or R_3 may also be an oxygen-containing group, the oxygen atom being protected by means of a hydrolysable group, is hydrolysed and dehydrated to form compounds according to the present invention. Preferably, the dehydration and the hydrolysis is carried out in one stage. The temperature at which said step is carried out is in general between t0 and 90 °C; the reaction time is usually 15 minutes to 4 hours. The dehydration/hydrolysis stage is carried out in a manner known per se and with agents known per se, such as, for example, with acetic acid or with HCl in acetone.

The invention is explained by reference to the following examples.

Example 1

a. A solution of 13.7 g of sodium borohydride in a mixture of 130 ml of methanol and 18.5 ml of 1M sodium hydroxide solution was added dropwise at room temperature to a solution of 60 g of 7β-methylestr-5(10)-ene-3,17-dione-3,3-dimethylacetal in 150 ml of tetrahydrofuran and a mixture of 75 ml of methanol plus 20 ml of 1M sodium hydroxide solution. After the reaction mixture had been stirred for 3 hours at room temperature, it was cooled to 0 °C and 75 ml of acetone was carefully added dropwise at a temperature of < +30 °C. Then the reaction mixture was poured out into 800 ml of water. Extraction with methylene dichloride yielded an organic layer which was washed until neutral with water, dried on sodium sulphate, filtered and evaporated to dryness in vacuo. Yield: 60 g of crude 17β-hydroxy-7β-methylestr-5-(10)-en-3-one-3,3-dimethylacetal.

b. 30 g of the product obtained in step 2a were dissolved in a mixture of 150 ml of tetrahydrofuran and 100 ml of methanol. After adding a solution of 10 g of oxalic acid dihydrate in 50 ml of water plus 50 ml of methanol, stirring was carried out for 1½ hours at room temperature. Then the reaction mixture was poured out into a solution of 20 g sodium hydrogen carbonate in 6 l of water. Extraction with methylene dichloride yielded an organic layer which was washed with water, dried on sodium sulphate and evaporated to dryness in vacuo. After purification by chromatography on silica gel, 20 g of virtually pure 17β-hydroxy-7β-methyl-oestr-5(10)-en-3-one were obtained. Crystallization from ethanol yielded pure substance.

c. 24.2 g of this product were dissolved in 250 ml of dry pyridine. 32 g of phenyltrimethylammonium tribromide were then added scoopwise at room temperature. After stirring for 2 hours at room temperature, the reaction mixture was poured out in 1.1 l of ice water, to which 50 ml of concentrated sulphuric acid was added. The precipitate was filtered, washed until neutral with water and dried in vacuo. Yield: 21 g of 17β-hydroxy-7β-methyl-oestr-4,9-dien-3-one. 18 g of pure compound were obtained by crystallization from diethyl ether.

d. A suspension of 40 g of the product obtained in stage 2c and 0.4 g of p-toluenesulphonic acid in 150 ml of ethylene glycol and 60 ml of triethyl orthoformate was stirred for 2 hours at room temperature. Working up of the reaction mixture by neutralization with triethylamine and extraction with methylene dichloride yielded, after purification by chromatography on silica gel, 34.4 g of virtually pure 17β-hydroxy-7β-methyloestr-5(10),9(11)-dien-3-one-3-ethyleneacetal.

e. 11.6 g of solid sodium hydrogen carbonate and 15.8 g of m-chloroperbenzoic acid were added consecutively scoopwise at -35 °C to a cooled solution of 22 g of 17β-hydroxy-7β-methyloestr-5(10),9(11)-dien-3-one-3-ethyleneacetal in 350 ml of methylene dichloride. After being stirred for 1 hour at -35 °C, the reaction mixture was diluted with a saturated sodium hydrogen carbonate solution followed by extraction with methylene dichloride. The organic layer was washed with 0.2M sulphite solution and with water until neutral, dried on sodium sulphate, filtered and evaporated to dryness in vacuo. After purification by chromatography through silica gel, 8.8 g of 5α,10α-epoxy-17β-hydroxy-7β-methyloestr-9(11)-en-3-one-3-ethyleneacetal were obtained.

f. 1.27 g of copper(I) chloride were added while stirring in a nitrogen atmosphere and at a temperature of -10 °C to a solution of p-dimethylaminophenylmagnesium bromide in dry tetrahydrofuran prepared from 3.1 g of magnesium turnings, 135 ml of dry tetrahydrofuran and 25.7 g of p-bromodimethylaniline. After stirring for 30 min. at -10 °C, a solution of 11.8 g of 5α,10α-epoxy-17β-hydroxy-7β-methyloestr-9(11)-en-3-one 3-ethyleneacetal in 150 ml of dry tetrahydrofuran was added. The reaction mixture was stirred for 2½ hours at room temperature, then cooled to 0 °C and carefully decomposed with a saturated ammonium chloride solution. Extraction with methylene chloride yielded an organic layer which was washed until neutral with water, dried on sodium sulphate, filtered and evaporated to dryness in vacuo. After purification by chromatography on silica gel, 11.8 g of 11β-(4-dimethylaminophenyl)-5α-17β-dihydroxy-7β-methyloestr-9-en-3-one-3-ethyleneacetal were obtained.

g. 5 g of aluminium isopropylate were added while stirring and in a nitrogen atmosphere to a solution of 8.8 g of 11β-(4-dimethylaminophenyl)-5α-17β-dihydroxy-7β-methyloestr-9-en-3-one-3-ethyleneacetal in 50 ml of dry cyclohexanone and 335 ml of dry toluene. After being stirred at reflux temperature for 2 hours, the reaction mixture was cooled to room temperature and a solution of 30 g of Seignette salt in 300 ml of water was added. Then the mixture was subjected to a steam distillation followed by extraction with methylene dichloride. The organic layer was washed until neutral with water, dried on sodium sulphate, filtered and evaporated to dryness in vacuo. After purification by chromatography on silica gel, 6.7 g of virtually pure 11β-(4-dimethylaminophenyl)-5α-hydroxy-7β-methyloestr-9-ene-3,17-dione-3-ethyleneacetal were obtained.

h. A solution of 21.0 g of propargyl alcohol tetrahydropyranyl ether in 120 ml of dry tetrahydrofuran was added dropwise in 15 minutes to a solution of ethyl-magnesium bromide prepared from 3.0 g of magnesium turnings and 10.2 ml of ethyl bromid in 110 ml of dry tetrahydrofuran.
After stirring for 30 minutes, a solution of 13.9 g of 11β-(4-dimethylaminophenyl)-5α-hydroxy-7β-methyloestr-9-ene-3,17-dione-3-ethyleneacetal in 90 ml of dry tetrahydrofuran was added dropwise.
After being stirred for 3 hours at room temperature, the reaction mixture was poured out into 500 ml of a 10% NH_4Cl solution and extracted with methylene dichloride. The organic layer was washed until neutral with water, dried on sodium sulphate, filtered and evaporated to dryness in vacuo. After chromatography of the residue on silica gel, 13.4 g of 11β-(4-dimethylaminophenyl)-5α-17β-dihydroxy-7β-methyl-17α-(3-t rahydropyranyloxy-1-propynyl)oestra-9-en-3-one- 3-ethyleneacetal were obtained.
i. 13.4 g of the product obtained in stage 1h were dissolved in 200 ml of a 70% acetic acid solution and h ated at 50 °C for 2½ hours. After neutralization with sodium hydrogen carbonate, extraction was carried out with methylene dichloride. The organic layers were washed until neutral, dried on sodium sulphat , filtered and evaporated to dryness in vacuo. Yield: 10.1 g of crude 11β-(4-dimethylaminophenyl)-17β-hydroxy-17α-(3-hydroxy-1-propynyl)-7β-methyloestra-4,9-dien-3-one. $[\alpha]_D^{20}$ = + 352° (c = 1, dioxane).

Example 2

3.5 g of 11β-(4-dimethylaminophenyl)-17β-hydroxy-17α-(3-hydroxy-1-propynyl)-7β-methyloestra-4,9-dien-3-one were dissolved in 250 ml of absolute ethanol and hydrogenated in the presence of 2.8 g of Lindlar catalyst until 1 equivalent of hydrogen had been absorbed (1.5 hours). The catalyst was filtered off and th filtrate was evaporated to dryness in vacuo. After chromatographing on silica gel, 11β-(4-dimethylaminophenyl)-17β-hydroxy-17α-(3-hydroxy-1-(Z)-propenyl)-7β-methyloestra-4,9-dien-3-one was obtained. $[\alpha]_D^{20}$ = + 426° (c = 1, dioxane).

Example 3

A solution of 2 g of 11β-(4-dimethylaminophenyl)-17β-hydroxy-17α-(3-hydroxy-1-propynyl)-7β-m thyloestra-4,9-dien-3-one in 200 ml of a 1/1 mixture of toluene and ethanol was hydrogenated in the presence of 200 ml of 5% Pd-$BaSO_4$ until 2 equivalents of hydrogen had been absorbed. The catalyst was filtered off and the filtrate evaporated to dryness. Chromatography on silica gel yielded 11β-(4-dimethylaminophenyl)-17β-hydroxy-17α-(3-hydroxy-1-propyl)-7β-methyloestra-4,9-dien-3-one. $[\alpha]_D^{20}$ = + 404° (c = 1, dioxane).

Example 4

A solution of 10 g of 11β-(4-dimethylaminophenyl)-17β-hydroxy-17α-(3-hydroxy-1-propyl)-7β-m thyloestra-4,9-dien-3-one in 200 ml of methylene dichloride was added to a stirred suspension of 15 g of pyridinium chlorochromate in 200 ml of methylene dichloride. The mixture obtained was stirred for 30 min. at 20 °C, diluted with 400 ml of ether and filtered through hyflo. The filtrate was concentrated and chromatographed on silica gel. In this manner, 4.5 g of 11β-(4-dimethylaminophenyl)-17β-hydroxy-7β-m thyl-17α-(3-oxopropyl)oestra-4,9-dien-3-one were obtained, very predominantly in the form of the cyclic h miacetal. This product was dissolved in 400 ml of toluene and after 45 g of silver carbonate/Celite (F tizon's reagent) had been added, it was boiled for 5 hours under reflux. Then 22.5 g of silver carbonate/Celite was again added and boiling was continued for 2 hours. The reaction mixture was cooled, filt red and evaporated to dryness. The residue was chromatographed on silica gel, 11β-(4-dimethylaminophenyl)-17β-hydroxy-7β-methyl-3-oxo-19-nor-17°-pregna-4,9-diene-21-carboxylic acid gamma-lactone being obtain d. $[\alpha]_D^{20}$ = + 394° (c = 1, dioxane); mp 145°C

Example 5

0.6 g of p-toluenesulphonyl chloride was added to a solution of 1.2 g of 11β-(4-dimethylaminophenyl)-17β-hydroxy-17α-(3-hydroxy-1-propyl)-7β-methyl-$\Delta^{4,9}$-oestra-dien-3-one in 15 ml of pyridine. After stirring for 6 hours, 100 ml of water was added, after which the mixture obtained was extracted with ether. The extracts were washed 5 times with water, dried on anhydrous Na_2SO_4 and evaporated to dryness. The residue was chromatographed on silica gel using toluene/ethyl acetate 1/1. This yielded 0.7 g of pure 11β-(4-dimethylaminophenyl)-7β-methyl-4',5'-dihydrospiro[estra-4,9-diene-17,2'(3'H)-furan]-3-one. $[\alpha]_D^{20}$ = + 426° (c = 1, dioxane); mp 154 °C.

Example 6

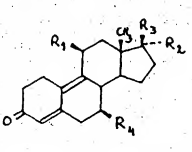
Analogous to Examples 1 h, I i and 3 was prepared: 11β-(4-dimethylaminophenyl)-17β-hydroxy-17α-(4-hydroxy-1-butyl)-7β-methyloestra-4,9-diene-3-one as an amorphous powder. $[\alpha]_D^{20}$ = + 376. (c = 0.5, dioxane), through reaction of 11β-(4-dimethylaminophenyl)-5α-hydroxy-7β-methyloestr-9-ene-3,17-dione-2-ethyleneacetal and 4-tetrahydropyranyloxy-1-butynylmagnesiumbromide, followed by hydrogenation and acid treatment.

Example 7

Analogous to example 6 was prepared 11β-(4-dimethylaminophenyl)-7β-methyl-3',4',5',6'-tetrahydrospiro[estr-4,9-diene-17,2'(2'H)-pyran]-3-one. $[\alpha]_D^{20}$ = + 408° (c = 0.5, dioxane) from 11β-(4-dimethylaminophenyl)-17β-hydroxy-17α-(4-hydroxy-1-butyl)-7β-methyloestra-4,9-diene-3-one.

Claims

1. 11-Arylsteroids, characterized in that said steroids have the following structure:



in which

R_1 is an aryl group with a  group as substituent,

X and Y each being separately H or a (1-4 C) hydrocarbyl group or together a (2-6 C) hydrocarbyl group which forms a 3- to 7-membered ring together with the nitrogen atom;

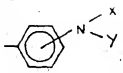
R_2 is hydrogen, hydroxyl, an acyloxy or an alkoxy group or a saturated or unsaturated hydrocarbyl group containing 1-8 carbon atoms, which hydrocarbyl group is provided with at least one hydroxyl, oxo, azido, cyano and/or halogen group;

R_3 is hydroxyl, an acyloxy or an alkoxy group or an acyl group optionally substituted by a hydroxyl, alkoxy, acyloxy or halogen group; or R_2 and R_3 together form a ring system, with the proviso that if R_3 is hydroxyl, R_2 is not hydrogen or hydroxyl; and

R_4 is a methyl or thyl group;

and th α- and β-bonds ar indicated by dashed (---) and wedged (◄) lines r spectively.

2. Compounds according to claim 1, charact rized in that R_1 is an aminophenyl group having th structure



X and Y each separately representing a saturated alkyl group containing 1-3 carbon atoms.

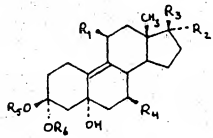
3. Compounds according to claims 1 or 2, characterized in that R_2 is a saturated or unsaturated alkyl group containing 1-4 carbon atoms substituted at least by one hydroxyl or oxo group.

4. Compound according to claims 1 or 2, characterized in that R_2 and R_3 form a 5- or 6-ring system.

5. Compounds according to claims 1-3, characterized in that R_3 is a hydroxyl group, a (1-6 C) acyloxy group or a (1-6 C) alkoxy group.

6. Compounds according to claims 1-5, characterized in that R_4 is a methyl group.

7. Process for preparing compounds according to claim 1, characterized in that a compound having the formula:



in which R_1, R_2, R_3, and R_4 have the same meaning as in claim 1, provided that, if R_2 and/or R_3 represent an oxygen-containing group, R_2 and/or R_3 may also be an oxygen-containing group, the oxygen atom being protected by means of a hydrolysable group, and wherein R_5 and R_6 represent an alkyl group containing 1-4 carbon atoms or R_5 and R_6 together represent an alkylene group containing 2-5 carbon atoms, is hydrolysed and dehydrated to form compounds according to claim 1 and in that hydroxyl groups optionally present at the position 17α or 17β of the compounds obtained are, if desired, esterified or in that a hydroxyl group optionally present at position 17β of the compounds obtained is, if desired, cyclized with an oxygen-containing group optionally present at position 17α.

8. Pharmaceutical preparation, characterized in that the active constituent consists of one or more substances according to claim 1 admixtured with a pharmaceutically acceptable carrier.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 88 20 2678

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
D,X	GB-A-2 175 905 (C. ERBA) * Claims * ---	1-8	C 07 J 41/00 A 61 K 31/565 A 61 K 31/58
A	EP-A-0 190 759 (SCHERING AG) * Claims * ---	1,8	
A	EP-A-0 057 115 (ROUSSEL-UCLAF) * Claims * -----	1,8	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

C 07 J 41/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	06-03-1989	HENRY J.C.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
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